REMARKS

Claims 1-10, 13, 15, 30-33, 36, 43 and 50 were pending in the subject application. Applicants respectfully note that claim 1 has been amended. This amendment does not involve any issue of new matter. Applicants respectfully request entry of the subject amendment such that claims 1-10, 13, 15, 30-33, 36, 43 and 50 will be pending.

Double Patenting

Claims 1-10, 13, 15, 30-33, 36, and 43-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Pat. No. 5,834,188. Without conceding the correctness of this rejection, Applicants will consider submitting a terminal disclaimer, if necessary, to obviate this rejection upon the indication of allowable subject matter.

Rejection Under 35 U.S.C. § 103

Claims 1,13, 36, 43, 45-47, and 49 are rejected under 35 U.S.C. 103(a), as being unpatentable over Foulkes *et al.* in view of Smart *et al.*

Applicants traverse the Examiner's rejection. MPEP 706.02(j) sets forth three basic criteria needed to establish a *prima facie* case of obviousness: 1) the prior art references must teach or suggest all the claim limitations; 2) some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) a reasonable expectation of success is required.

A. References do not teach or suggest all claim limitations

First, applicants contend that the combined teachings of Foulkes and Smart do not teach or suggest all the claim limitations of claim 1, nor claims 13, 36, 43, 45-47 and 49 which are dependent from claim 1.

Claim 1 recites, in part, as follows:

"A method for identifying a compound that induces a biological effect mediated by a morphogen selected from OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vg1, Vgr-1, DPP, or 60A, the method comprising:

(a) providing a test cell comprising a DNA comprising:

(1) a transcription activating element responsive to said morphogen, and

(2) a reporter gene encoding a detectable gene product, the transcription activation element being in operative association with the reporter gene,

wherein the reporter gene present in the DNA is transcribed when the DNA present in a cell that is

(1) responsive to the morphogen, and

(2) contacted with said morphogen;" (Emphasis added)

Accordingly, the method of claim 1 includes, among other things, two features emphasized for purposes of this discussion. First, the method is for identifying a compound which induces a biological effect mediated by a molecule *i.e.* a morphogen. Secondly, the method comprises the use of a specific type of transcription activating element *i.e.* one that is responsive to a morphogen. Accordingly, Claim 1 relates to a method where the biological effect and the transcriptional activating element are limited by their respective relationship to a molecule, in this case a morphogen. Claim 1 does not relate to isolating just any type of compound or to a compound having just any type of biological effect, or to using just any type of transcription activating element. As discussed in more detail below, the combined teachings of the cited references do not teach or suggest a method having the specific biological effects or the specific transcriptional activating element, and thus do not teach or suggest every limitation of claim 1. Accordingly, the Examiner has not made a case of prima facie obviousness.

1. Failure of cited references to teach or suggest a method of isolating a compound that induces a biological effect mediated by a morphogen

As stated above, claim 1 recites a method for identifying a compound that induces a biological effect mediated by a morphogen, a limitation which is not taught or suggested by a combination of the cited references.

In interpreting the teachings of Foulkes, and in particular claim 1 therein, the Examiner alleges on page 4, lines 7-11 of the Office Action, that "Foulkes teaches a method for identifying a compound that induces a biological effect (column 73, lines 40-43) comprising a) providing a test cell comprising a DNA defining a transcription activating element operatively linked to a

reporter gene encoding a detectable gene product, which, when present in a responsive cell contacted with a compound serves to induce a transcription of said reporter gene..." (emphasis added).

Applicants note that the section of Foulkes cited by the Examiner, column 73, lines 40-43, specifically recites as follows:

> A method of determining whether a chemical not previously known to be a modulator of protein biosynthesis specifically transcriptionally modulates a gene-of-interest which comprises:

Contrary to the Examiner's allegation, this section of Foulkes does not mention or describe a chemical having biological effect, much less a biological effect mediated by another molecule, such as a morphogen. Rather, the method of Foulkes is directed to identifying a chemical that interacts with (i) a transcriptional regulatory sequence or (ii) a promoter of interest to yield expression of a reporter gene, but is silent as to inducing any biological effect for the chemical, much less inducing a biological effect mediated by another molecule. Accordingly, Foulkes is deficient since it does not teach or suggest an element of claim 1.

Even if Foulke were to teach or suggest the induction of a biological effect for the chemical that is screened, which it does not, the biological effect would be of interacting with the transcriptional regulatory sequence or the promoter of the gene-of-interest, or of specifically transcriptionally modulating a gene-of-interest. However, even if this were the case, Foulkes fails to teach or suggest a chemical or compound having the biological effect of a second molecule, much a less of a second molecule to which the regulatory sequence is responsive to a morphogen. Thus, Foulkes is further deficient since it fails to teach or suggest another element of claim 1 relating to a specific biological effect of the compound.

The teachings of Smart fail to remedy the deficiencies of Foulkes. Smart does not teach or suggest compounds having the biological effect mediated by a morphogen. Smart describes methods of screening candidate compounds for the ability to modulate the level of a morphogenic protein. Smart teaches that the molecule-of-interest is a morphogen, as this is the molecule whose protein levels are to be altered by the compounds that are screened. When the teachings of Smart and Foulkes are combined, one with routine skill in the art will apply the method of Foulkes with the protein-of-interest being a morphogen as taught by Smart. However, no biological effect mediated by a morphogen is taught or suggested by the combined teachings.

If the combined teachings taught or suggested any type of biological effect for the compounds that are isolated, it would be the biological effect of a hypothetical unknown molecule that promotes morphogen protein expression, rather than of a biological effect mediated by a morphogen itself.

Accordingly, the Examiner has failed to show that the cited references, alone or in combination, teach or suggest certain elements of claim 1, *e.g.* the identification of a compound having the biological effect mediated by morphogen, and thus the Examiner has not made a case of prima facie obviousness.

2. Failure of cited references to teach or suggest a method comprising the use of a transcriptional regulatory element responsive to a morphogen

The cited references also fail to describe another element of claim 1. Claim 1 recites the use of a DNA comprising "a transcription activating element responsive to said morphogen" (Emphasis added). Foulkes only teaches that the transcription activating element, referred therein as a transcriptional regulatory sequence, be from the gene-of-interest (column 73, line 51). However, the claimed methods of the subject application recite the use of a transcriptional regulatory sequence that is responsive to the morphogen. A transcriptional regulatory sequence from a morphogen *i.e.* that of cited art and one that is responsive to a morphogen *i.e.* that of the claimed invention, are distinct. Thus, the methods described in Foulkes do not teach or suggest a transcriptional regulatory sequence that is responsive to anything, let alone to a morphogen.

Not only does Foulkes alone fail to teach or suggest the claimed invention, but the combined teachings of Foulkes and Smart also fails to teach or suggest a transcriptional regulatory sequence that is responsive to a morphogen. Smart describes methods of screening candidate compounds for the ability to modulate the level of a morphogenic protein, but not of modulating the expression of genes which are themselves regulated by morphogens.

Assuming, *arguendo*, that Foulkes and Smart could be combined, that combination would be, at most, the screening method of Foulkes, which requires a transcriptional regulatory sequence from the gene-of-interest, and the gene-of-interest being the morphogenic proteins described in Smart. In other words, the method of screening for candidate compounds that increase the expression of morphogens, as taught by Smart, would be modified with the teachings of Foulkes by "replacing" the coding region of a morphogen by that of a reporter gene,

such that the detection of agents which regulate morphogen expression would be facilitated by the reporter gene.

Thus, one combining the methods described in Smart for identifying compounds that increase morphogen proteins levels with the screening methods described in Foulkes would arrive, at best, at a method of screening compounds using a transcriptional regulatory sequence from a morphogen, such as an enhancer element of OP-1, operably linked to a reporter transgene. Contrary to the Examiner's allegations, Smart does not teach or suggest that the transcriptional regulatory elements used be responsive to morphogens in the screening method of Foulkes. In fact, Smart is completely silent as to use of any kind of transcriptional regulatory sequences.

Thus, the examiner has failed make a *prima facie* case of obviousness according to the requirements described in MPEP 706.02, because among other things, the combined teachings of Foulkes and Smart do not teach or suggest the subject matter of claim 1, taken as a whole, or of its dependent claims. Accordingly, applicants respectfully request reconsideration of this ground of rejection.

3. Failure of cited references to teach or suggest all the features of the dependent claims 6, 9, 33 and 44

Not only does the combination of all cited references fail to teach or suggest all the features of the independent claims of the present invention, but additional features recited in the dependent claims are also not taught or suggested by the cited references. Morever, even if these additional features were taught or suggested, the Examiner has not set forth the basis for such in the Office Action. These dependent claims include the following:

a) Claim 6, which recites a morphogen responsive transcription activating element which comprises a sequence of A and T residues, and claims 7 and 8 which are dependent on claim 6.

b) Claim 9 which recites the method of claim 6 wherein the A and T residues are adjacent to an AP-1 biding site sequence, and claim 10 which is dependent on claim 9.

c) Claim 33, which recites the method of claim 1, 2, 15 or 30 comprising part of a medium or high-flux screening assay.

d) Claim 44, which recites the method of claim 2, wherein said morphogen-responsive

transcription activating element also binds with a second protein having general DNA-binding properties of an AP-1 family protein.

Applicants request that if the Examiner maintains his obviousness rejections to the above dependent claims or to any other dependent claims in a future Office Action, that the Office Action describe for each dependent claim rejected, as required by MPEP 706.02(j), (1) how the prior art references teach or suggest all the claim limitations; 2) a motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) reasonable expectation of success for arriving at the claimed invention.

B. Lack of Motivation to Combine References

Not only has the Examiner failed to show that the cited references teach or suggest all the claimed subject matter, but the Examiner has failed to show a motivation to even attempt to combine the teachings of Foulkes and Smart.

The Examiner alleges on page 5, lines 9-13 of the Office Action that "it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to apply the method of Foulkes to the screening of compounds which induce morphogenesis since Smart expressly notes the desirability of screening compounds for their ability to modulate morphogenesis (see column 2, lines 61-64, abstract, column 15, lines 55-64, especially." (Emphasis added). Applicants have examined the three sections of Smart recited by the Examiner in support of his argument to combine the references, and find no evidence of screening compounds for their ability to modulate morphogenesis.

(i) The first of these sections, column 2, lines 61-64, recites as follows "The invention features a method of screening candidate compounds for their ability to modulate the effective local or systemic concentration or level of morphogenic protein in an organism" (emphasis added). Applicants find no mention of modulation of morphogenesis as alleged by the Examiner. Instead, this section relates to testing of these compounds in vivo for their ability to modulate the expression of morphogen proteins in an organism, and not for testing their ability to modulate a developmental phenotype such as morphogenesis.

(ii) The second of these sections, the abstract, recites as follows: "Disclosed is a method

of screening candidate compounds for the ability to modulate the level of morphogenic protein in mammalian system. The method includes determining a parameter indicative of the level of production of a morphogenic in a cell culture known to produce the morphogen, incubating a candidate compound with the culture for a time sufficient to allow the compound to affect the production of the morphogenic protein, and then assaying the culture again to detect a change in the level of morphogenic protein production."

Again, contrary to the Examiner's allegations, the abstract fails to note any desirability for screening compounds for their ability to modulate morphogenesis. The abstract merely describes the measurement of levels of morphogenic protein production and not morphogenesis.

(iii) The third of these sections, column 15, lines 55-64, recites as follows: "The other assay of the invention involves screening candidate compounds for their ability to modulate the effective systemic or local concentration of a morphogen by incubating the compound with a cell culture that produces the morphogen, and assaying the culture for a parameter indicative of a change in the production level of the morphogen. Useful candidate compounds then may be tested for in vivo efficacy in a suitable animal model. These compounds then may be used in vivo to modulate effective morphogen concentrating in the disease treatment." Again, this section of Smart referenced by the Examiner fails to note any screening of compounds for their ability to modulate morphogenesis. Instead, the section calls for testing whether the candidate compounds are effective in changing the production level of a morphogen *in vivo* and in disease treatment, with no specific mention of morphogenesis or of any morphogenesis-based diseases. Accordingly, Smart does not teach or suggest a desirability of screening compounds for their ability to modulate morphogenesis.

Applicants have shown that the three sections of Smart which the Examiner uses to support the alleged desirability of screening compounds for their ability to modulate morphogenesis does not provide sufficient motivation to combine Foulkes with Smart. Because the Examiner has not presented a motivation to combine these references, a case of prima facie obviousness as set forth in MPEP 706.02(j) has not been made. Therefore, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Furthermore, applicants note that even if Smart had provided a motivation to apply the method of Foulkes to the morphogenesis (which applicants do not concede), one of ordinary skill in the art would have merely taken a transcriptional regulatory sequence derived from a

morphogen and operably linked it to a reporter in order to isolate compounds that would alter the expression level of the reporter, as described above in section A, with the hope of identifying a compound that changes the expression level of a morphogen protein. However, there would not have been any reasonable expectation of success because, among other things, the transcriptional regulatory sequences of morphogens themselves of the signaling pathways that could modulate their expression, and thus provide targets for the chemicals, were not clearly delineated in the art. Thus, the cited references do not render obvious the claimed invention.

C. Combination of Foulkes and Smart with additional references

The Examiner bases his rejection of claims 1-3, 6, 9, 13, 36, 43-47, and 49 under 35 U.S.C. 103(a) on the combined teaching of Foulkes and Smart, further in view of Nadal-Ginard. Nadal-Ginard does not overcome the defects of the combined teachings of Foulkes and Smart as described above on pages 7-10. At most, Nadal-Girard may teach the isolation of agents which promote or decrease cell proliferation by screening for agents which modulate the binding of MEF proteins to pocket proteins, using in some enbodiments reporter genes. However, Nadal-Ginard fails to teach or suggest a (i) method of isolating a compound that induces a biological effect mediated by a morphogen or (ii) the use of transcriptional regulatory elements which are responsive to a morphogen to identify compounds that induce the biological effect of the morphogen. Since Nadal-Ginard combined with Foulkes and Smart fails to teach all the elements of the instant claims, a case of prima facie obviousness has not been presented by the Examiner with regards to claims 1-3, 6, 9, 13, 36, 43-47, and 49. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Similarly, the Examiner bases his rejection of claims 1, 13, 36, 43, and 45-50 under 35 U.S.C. 103(a) depends on combined teaching of Foulkes and Smart, further in view of Ozkaynak. Ozkaynak does not overcome the defects of the combined teachings of Foulkes and Smart as described above on pages 7-10. At most, Ozkaynak may teach the identification of molecules which increase morphogen protein expression, like Smart, but does not teach or suggest for example, transcriptional regulatory elements which are responsive to a morphogen. However, Ozkaynak fails to teach or suggest a (i) method of isolating a compound that induces a biological effect mediated by a morphogen or (ii) the use of transcriptional regulatory elements which are responsive to a morphogen to identify compounds that induce the biological effect of

the morphogen. Since Ozkaynak combined with Foulkes and Smart fails to teach all the elements of the instant claims, a case of prima facie obviousness has not been presented by the Examiner with regards to claims 1, 13, 36, 43, and 45-50. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

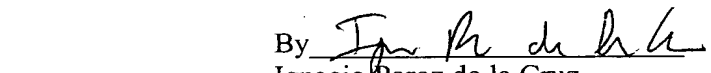
CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Please charge our Deposit Account No. 18-1945, under Order No. JJJ-02-540, for the requisite fee for a one-month extension from which the undersigned is authorized to draw. Applicants note that the subject application is entitled to small entity status as reflected by the small entity status filed with the application and the indication on the application transmittal form, as well as payment of a small entity fee on July 10, 2000. Accordingly, even though certain fees have inadvertently been paid at the large entity rate, Applicants contend that the application was and still is entitled to small entity status. Accordingly, the fee for the extension of time is being paid at the small entity rate of $55. Applicant believes no additional fee is due with this response. However, if a fee is due, please charge our deposit account above for any such fees.

Dated: February 6, 2004

Respectfully submitted,

By 

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